REMARKS

Status of the Application

Claims 1-9 were filed in the application. The Office withdrew claims 4-9 from consideration, as drawn to non-elected subject matter, leaving claims 1-3 under examination. With this Amendment, Applicants have amended claims 1-3 and added new claims 10-20. Thus, amended claims 1-3 and new claims 10-20 are now pending and under examination.

Claim 1 is amended to recite, "A mutant kanamycin nucleotidyltransferase comprising the sequence of SEQ ID NO:1 modified by at least one point mutation selected from . . ." This amendment is supported by the application as a whole, for example, Example 2 at pages 11-12; and Table 1 at page 13.

The phrase "improved thermostability" in claims 1-3 is changed to, "improved thermostability as compared to SEQ ID NO:1." This amendment is also supported by the application as a whole, for example, at Figure 2.

New claim 10 is added, and states "A mutant kanamycin nucleotidyltransferase having kanamycin nucleotidyltransferase activity comprising the sequence of SEQ ID NO:1 modified by at least one point mutation selected from Met57Leu, Ala62Val, Ser94Pro, Ser203Pro, Asp206Val, His207Gln, Ser220Pro, Ile234Val, and Thr238Ala, and having improved thermostability as compared to SEQ ID NO:1, wherein the sequence of SEQ ID NO:1 is not modified by any other mutations." This claim is

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supported by the specification as a whole, for example in originally filed claim 1 at page 20.

New claims 11-19 add dependent claims to specific embodiments of the invention. These claims are supported by the application as a whole. Particular support may be found at page 11, Example 2 and page 13, Table 1.

New claim 20 states, "The mutant kanamycin nucleotidyltransferase according to claim 1, wherein the mutant kanamycin nucleotidyltransferase contains from 1 to 19 point mutations when compared to SEQ ID NO:1." This claim is supported by the application as a whole, in particular at page 16, lines 3 to 6.

Applicants submit that these claim amendments are fully supported by the specification, do not introduce new matter or require a further search of the art, and respectfully request their entry.

Applicants acknowledge the grant of priority benefit of Japanese Application No. 309616/1999 filed October 29, 1999. Applicants also thank the Examiner for indicating that she has considered the references submitted in the IDS by initialing the 1449 form.

Objection to the Drawings

The Office objected to Fig. 1 as informal under 37 C.F.R. § 1.85(a). (Office Action at page 3.) Applicants submit a formal version of Fig. 1 at Tab C, and respectfully request the withdrawal of this objection.

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Objections to the Specification

The Office objected to the Abstract for failing to completely describe the disclosed subject matter. Applicants respectfully traverse, particularly the suggestion that the abstract "is crucial in defining the disclosed subject matter." Indeed, 37 C.F.R. § 1.72 and M.P.E.P. § 608.01(b) provide that the abstract will not be used to interpret the scope of the claims. However, Applicants have submitted a revised abstract at Tab B incorporating the Examiner's suggestions at page 4 of the Office Action merely to facilitate prosecution. This abstract does not limit the scope of the claimed invention in any way.

The Office also objected to the specification, alleging that SEQ ID NOS:12-20 were not mentioned in the text or in the claims. Applicants note, however, that SEQ ID NOS:12-20 correspond to sequences in Table 1 in the specification as filed. To facilitate prosecution, a substitute Table 1 including specific reference to SEQ ID NOS:12-20 is set forth at Tab A. Because these sequences were fully disclosed in Table 1 as filed, and Applicants are only providing sequence reference numbers,

Applicants submit that this amendment does not introduce new matter.

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Claim Objections under 37 C.F.R. § 1.75(c)

The Office objected to claim 3 under 37 C.F.R. § 1.75(c), as being of improper dependent form. Applicants note that independent claim 1 has been amended such that dependent claim 3 further limits the subject matter of claim 1, thus rendering this objection moot.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

The Office rejected claim 1 under 35 U.S.C. § 112, second paragraph, alleging that it is indefinite. The Office contended that the scope of claim 1 could be interpreted in more than one way. (Office action at page 5.) Applicants acknowledge that the Examiner has pointed out two possibilities, and have amended the claims to cover both interpretations. Claim 1 has been amended to include additional mutations beyond the point mutations explicitly listed, while new claim 10 includes the phrase, "wherein the sequence of SEQ ID NO:1 is not modified by any other mutations."

Additionally, the Office alleges that the phrase "as against . . . SEQ ID NO:1" in claim 1 is unclear, especially when the protein contains additional mutations. (Office action at page 5.) However, in the specification, Table 1, page 13, Applicants have disclosed an alignment of the functional residues mutated in 10 KNT mutants which contain mutations including the point mutations listed in claim 1 as well as other point mutations. Therefore, one of skill in the art would be able to align the sequences of claim 1 as was done for the sequences in Table 1.

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The Office questions the definition of the word "mutant." (Office action at page 6.) Applicant is operating under the assumption that the Office is unclear whether or not a naturally occurring variant of KNT qualifies as a "mutant." Applicants note that the word "mutant" is defined relative to SEQ ID NO:1—thus whether the mutation is naturally occurring or isolated in a laboratory is irrelevant. Applicants have added the term "isolated" to distinguish only from any mutant proteins that may be existing in nature.

Additionally, the Office indicated that Met in the phrase "Met57Leu" was irrelevant for composition claims. Applicants note that "Met57Leu" is a standard way to articulate a point mutation and helps the skilled artisan understand which positions to mutate. The 57 provides the position where the Leu will be substituted. The Met provides a confirmation that the mutation is occurring at the correct position. Applicants believe this terminology is clear to one of ordinary skill in the art. However, merely to facilitate prosecution, and not in acquiescence, the amended claim provides more explicit reference to SEQ ID NO:1.

The Office also asserted that the term "improved thermostability" in claims 1-3 is indefinite, alleging that the nature of the "wild type" enzyme used as the reference sequence in the instant claims is unclear. (Office action at page 6.) The Office contends that this lack of clarity arises because the specification discloses a naturally occurring *S. aureus* kanamycin nucleotidyltransferase (KNT) disclosed as SEQ ID NO:11 (WT) as well as a well characterized, heat stable KNT mutant disclosed as SEQ ID NO:1 (WT*). (Office action at page 6.) Applicants submit that the claims as filed are

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definite in describing SEQ ID NO:1 as a baseline "wild type" sequence for further mutation, since it is the wild type reference sequence disclosed in original claims 1 and 3. SEQ ID NO:1 is also used as the reference wild-type sequence in Example 1 at page 11, in Table 1 at page 13, in Table 3 at page 16 and in Example 4 at pages 16 and 17. However, to facilitate prosecution and not in acquiescence, Applicants have replaced "improved thermostability" with "improved thermostability as compared to SEQ ID NO:1," in amended claim 1. In light of the amendments described above, Applicants respectfully request the withdrawal of these rejections.

Claim Rejections under 35 U.S.C. § 112, First Paragraph, Written Description

The Office rejected claim 1 as allegedly lacking written description support. The Office stated that "[a]ny KNT having any structure is encompassed by the claimed scope. Such proteins are only described by limited functional characteristics. . . " (Office Action at page 8.) Further, it contends that "no structural relationship is described among KNT species or is used in the claims." (Office action at page 6.) Applicants respectfully traverse.

In discussing how to describe a genus sufficiently to meet the written description requirement, the Court of Appeals for the Federal Circuit states: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus. . . " *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997).

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This statement indicates that a sufficient number of representative sequences can define a genus.

Lilly also discusses the number of sequences required to define a genus. For example, in *Lilly*, a single sequence was found not to cover the claimed genera; further, *Lilly* cites *In re Gosteli*, 872 F.2d at 1012, 10 U.S.P.Q.2d at 1618 (Fed. Cir. 1989), in which the disclosure of two compounds was not sufficient to describe a broader subgenus. These cases suggest that more than two species are necessary to represent a genus. *Lilly* also cites *In re Angstadt*, 537 F.2d at 502-03, 190 U.S.P.Q. at 218 (C.C.P.A. 1976), in which "the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process." This suggests that a plurality of sequences is sufficient to define a genus.

Applicants have disclosed the amino acid sequences of ten mutant KNT sequences with improved thermostability as compared to SEQ ID NO:1. (SEQ ID NOS:12-20; SEQ ID NO:3.) Because the specification has a plurality of sequences representing the genus, it meets the criteria discussed in Lilly for defining a genus.

Furthermore, claim 1 restricts the scope of the genus by requiring the physical presence of at least one of the eight listed mutations to a base sequence of SEQ ID NO:1. These mutations thus represent common characteristics of the claimed molecules, since a KNT that does not contain any of the eight listed point mutations is not covered by the claims. Thus, unlike *Lilly*, where the claim language was exclusively functional, claim 1 provides a specific sequence requirement. This requirement permits one skilled in the art to readily exclude molecules beyond the scope of the genus.

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Applicants submit that, contrary to the Office's contention, Applicants have provided a sufficient number of representative species to claim the genus, and further have provided a common sequence requirement to limit the scope of the genus. In light of these remarks, Applicants respectfully request the withdrawal of the 35 U.S.C. § 112, first paragraph, written description rejection.

Claim Rejections under 35 U.S.C. § 112, First Paragraph, Enablement

The Office rejected claim 1 under 35 U.S.C. § 112, first paragraph, scope of enablement, alleging that claim 1 "does not reasonably provide enablement for KNTs having any sequence while retaining catalytic activity and improving thermostability." (Office action at page 8.)

The Office cited *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), as support for its rejection of Applicants' claims. The Office alleges that the specification does not provide guidance in determining whether or not a given mutation will produce a KNT with improved thermostability as compared to SEQ ID NO:1. Contrary to the Office's assertion, the specification does provide information on which mutations will be effective in the invention. Applicants note that the specification discloses that only one of the eight mutations listed in claim 1 (Ile234Val) is found in the hydrophobic core, while none of these eight mutations were found at the boundary of the dimer subunit. (page 17, line 30; page 18, lines 1-3; Figure 3.) New mutations in the hydrophobic core and in the boundary of the dimer subunit would thus be predicted not to improve KNT thermostability as compared to SEQ ID NO:1.

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Moreover, three of the listed mutations are proline substitutions, respectively found at a specific ß-turn (Ser94Pro), a specific surface loop (Ser203Pro), and a specific α-helix (Ser220Pro). (page 18, lines 6-12.) The specification thus discloses guidance in describing the types of mutations that would be predicted to influence thermostability.

Applicants also respectfully submit that the Office has failed to fully consider all of the enablement factors listed in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). M.P.E.P. § 2164.01(a) Concerning the quantity of experimentation necessary, determining if a given sequence is covered by the claim is simple matter of routine experimentation. Isolating and sequencing mutant KNT genes requires mutagenesis, cloning, and sequencing, common techniques in the art. Moreover, testing the thermostability of KNT is also a simple matter, and is taught throughout the specification. For example, pages 9 and 10 discuss a rapid procedure for KNT purification using sonification and column purification, and pages 10 and 11 teach a KNT activity assay using labeled ATP as well as a spectrophotometric method for monitoring heat denaturation.

Concerning the presence or absence of working examples, Applicants have provided the complete sequence of 10 species of mutant kanamycin nucleotidyltransferase with improved thermostability. (SEQ ID NOS:12-20, SEQ ID NO:3.) Finally, concerning the relative level of skill in the art, all of the techniques needed to generate, identify and characterize thermostable mutant kanamycin nucleotidyltransferases are routine and predictable procedures.

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Thus, based on the amount of guidance provided in the specification and in consideration of all of the *Wands* factors, Applicants respectfully request the withdrawal of the 35 U.S.C. § 112, first paragraph, enablement rejection.

Claim Rejections under 35 U.S.C. § 102(a)

The Office rejected claims 1-3 under 35 U.S.C. § 102(a) as allegedly being anticipated by Hoseki *et al.* (*J. Biochem.* 126(5):951-6 (1999)). The Office contended that Hoseki *et al.* was published in November, 1999, a date less than a year before the filing date of October 27, 2000, but after the claimed foreign priority date of October 29, 1999. The Office requested a translation of Japanese Application No. 309616/1999. As requested, Applicants submit a translation of the Japanese priority document along with the declaration of Ms. Yumi Naito who executed the translation of this document at Tab D. The Japanese priority document fully supports the claims in this application. Thus, Applicants respectfully request the withdrawal of this rejection.

Claim Rejections under 35 U.S.C. § 102(b)

The Office rejected claim 1 under 35 U.S.C. § 102(b), asserting at page 11 that Matsumura *et al.* anticipates claim 1. (*J. Biol. Chem.* 260(28):15298-303 (1985)). Specifically, the Office contended that Fig. 4 of Matsumura *et al.* allegedly "teaches the *S. aureaus* wildtype (SEQ ID NO:11) KNT enzyme having any one or more of several point mutations, particularly Ala62Val, induced by hydroxylamine treatment of the gene." (Office Action at page 11.)

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In an effort to facilitate prosecution and without surrendering any subject matter in this invention, claim 1 has been amended to remove the Ala62Val mutation from the list of point mutations. Thus, Applicants respectfully request the withdrawal of the 35 U.S.C. § 102(b) rejection.

Applicants note that new claim 10 lists the Ala62Val mutation present in Matsumura *et al*. Applicants point out, however, that Matsumura and coworkers mutated the wildtype (SEQ ID NO:11) KNT enzyme, while claim 10 includes the phrase, "the sequence of SEQ ID NO:1 is not modified by any other mutations." SEQ ID NO:1 is a heat stable kanamycin nucleotidyltransferase with different amino acids (D80Y and T130K) than SEQ ID NO:11. Because Matsumura et al. does not contain all of the elements of new claim 10 (i.e., because it contains other mutations), it cannot anticipate it. M.P.E.P. § 2131.01; V*erdegaal Bros. v. Union Oil. Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q. 2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of claims 1-3 and 10-20.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: January 7, 2003

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